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Development of Novel Antioxidants: Design, Synthesis, and Reactivity

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We are attempting to develop novel synthetic antioxidants aimed at retarding the effects of free-radical induced cell damage. In this paper we discuss the design strategy and report the synthesis of seven novel antioxidants, including six catechols and a benzylic phenol. The bond dissociation enthalpy (BDE) for the most active (weakest) OH bond in each molecule was calculated by theoretical methods, as well as the BDE for the semiquinone radical. Reaction rates with the nitrogen-centered free radical DPPH$^{\bullet}$ were measured in ethyl acetate. The log of k_{DPPH} for bimolecular reaction correlated well with the primary BDE. The correlation between rate constants and calculated BDEs shows that the BDE is a good predictor of antioxidant activity with DPPH$^{\bullet}$, suggesting that our design criteria are useful and that these compounds should undergo further testing in cell cultures and in animal models.

Introduction

There is currently under way a tremendous effort to study the properties of naturally occurring antioxidants because of their potential clinical significance. Thus free radicals generated in biological systems, particularly alkyl peroxyl (ROO$^{\bullet}$), which occurs in lipid peroxidation and superoxide ion (O_2^{-}), which is formed during normal metabolism, have been implicated in aging and in age-related degenerative diseases. Many authors have demonstrated protective effects of different chemical antioxidants in cellular systems, e.g. α-tocopherol and related compounds, ascorbic acid, the flavonoids, stilbenes related to resveratrol, catechins which occur naturally in tea, glutathione and related thiols, etc.[1] The antioxidants often work cooperatively, so that the radical derived from α-tocopherol reacts with ascorbic acid (low pH) or ascorbate ion (higher pH) to regenerate α-tocopherol. The ascorbyl radical that forms can then either disproportionate to ascorbate plus dehydroascorbic acid or be reduced back to ascorbic acid by interaction with other reducing species in the cell.[1]

There has been much less work on the systematic study of synthetic antioxidants designed to optimize the antioxidant activity, while at the same time satisfying other important criteria, including solubility, bioavailability, and lack of toxicity (or selective toxicity in the case of cancer chemopreventive antioxidants). Earlier work considered variations on the vitamin E polyalkylchromanol class of compounds, and was able to demonstrate some increase in antioxidant activity.[2,3] More general accounts on how to approach the problem were given by Thomas[4] and by Noriguchi and Niki.[5] Some of the present authors[6] recently described the synthesis of a new class of compounds, the naphthalene diols, which aimed to improve on the activity of such antioxidants while at the same time preventing toxicity due to quinone formation, and demonstrated enhanced reactivity with a nitrogen-centered test free radical, DOPPH$^{\bullet}$ (2,2-di(4-*tert*-octylphenyl)-1-picrylhydrazyl). DOPPH$^{\bullet}$ is a more lipid-soluble version of the related radical DPPH$^{\bullet}$ (2,2-diphenyl-1-picrylhydrazyl), which is widely used as a test radical. These authors were able to show rate enhancements for some naphthalene diols in heptane solution that were over 2 orders of magnitude larger than those for α-tocopherol, the standard reference compound.[6]

In designing synthetic antioxidants, it is helpful to consider what kind of molecular structure is optimum and what kind of design parameters are relevant to the problem.[2,5,7] Generally speaking compounds containing weak C−H bonds which lead to carbon-centered radicals R$^{\bullet}$ are undesirable, because such compounds usually rapidly add molecular oxygen and thus become chain propagating peroxyl radicals ROO$^{\bullet}$ (although some may

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(1) Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*; Oxford University Press: Oxford, UK, 1999.
(2) Burton, G.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *194*, 194−201.
(3) Mukai, K.; Okabe, K.; Hosose, H. *J. Org. Chem.* **1989**, *54*, 557−560.
(4) Thomas, C. E. In *Handbook of synthetic antioxidants*; Packer, L., Cadenas, E., Eds.; Marcel Dekker: New York, 1997; pp 1−52.
(5) Noguchi, N.; Niki, E. *Free Radicals Biol. Med.* **2000**, *28*, 1538−1546.
(6) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190−5196.
(7) Wright, J. S. *Chem. Br.* **2003**, *39*, 25−27.

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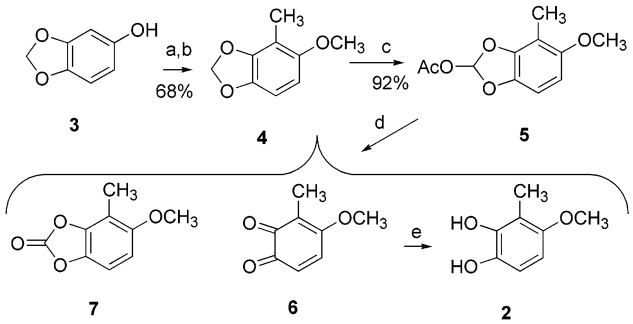
not).[8,9] Sulfur-centered radicals are of interest and play an important role in biochemistry, although they are also capable of forming peroxyl radicals of the type RSOO• by reaction with O_2.[1] Nitrogen-centered radicals are a possibility and can be stable with respect to oxygen addition, as in DPPH•, but by far the most studied molecules involve oxygen-centered radicals. The virtue of the latter is that oxygen-centered radicals (e.g. ArO−H → ArO•) do not react with oxygen to form a trioxyl radical ArOOO• since this step is endoergic by ca. 20 kcal/mol.[10] The second design point is that the molecule should react rapidly with peroxyl radicals. Since ROO• forms a bond in ROO−H with a bond dissociation enthalpy (BDE) of ca. 88 kcal mol^{-1}, this requires that an antioxidant ArO−H have a BDE below that value, to provide an exoergic and therefore rapid reaction. Since α-tocopherol has a (experimental) BDE of 77 kcal/mol[2], we should design an antioxidant with a BDE less than that value. Ascorbate ion has a BDE of 68.5 kcal/mol[11] and if ascorbate is to regenerate the synthetic ArO−H, its BDE must be less than that of ArO−H. This places the useful design window at about 68−75 kcal/mol. Third, the radical that is formed should be relatively unreactive with lipid, protein, or other biological substrates. Fourth, the antioxidant or radicals derived from it should not react with molecular oxygen at an appreciable rate to produce superoxide anion or its conjugate acid, hydroperoxyl radical (autoxidation). Finally, to design lipid-soluble antioxidants, it may be necessary to add functional groups whose only purpose is to improve solubility, e.g. the phytl tail in α-tocopherol, or to improve transport through the cell wall, e.g. by esterifying the alcohol groups.

In the present paper we describe the synthesis and testing of seven novel antioxidants, six of which fall into or near our design window and one that deliberately lies outside it. BDEs are calculated for first and second oxidations (i.e. for successive loss of H-atoms) for each, and it is shown that the log of the reaction rate constant with DPPH• correlates inversely with the primary BDE, as expected. Results are compared with the phenols and naphthalene diols described previously and it is shown that these novel compounds in general validate the reactivity predictions based on BDE.

Theoretical and Experimental Methods

Calculation of BDE and IP. For calculation of the BDE we used the lowest level method (LLM) described by DiLabio et al.[12] Details of this calculation, which uses a B3LYP density functional approach, are described in the Experimental Section. The BDE corresponds to the standard gas-phase enthalpy change at 298 K ($\Delta H°_{298}$) for ArO−H (g) → ArO• (g) + H• (g). In cases where there are two OH groups as in the catechols, we use the term BDE_1 for loss of the first (most weakly bound) H-atom to form the semiquinone and BDE_2 for loss of the second H-atom to form the quinone. Using this procedure[13,14] we obtained a BDE for phenol of 87.10 kcal mol^{-1} in good agreement with a current experimental gas-phase value of 87.3 ± 1 kcal mol^{-1} obtained by Wayner et al.,[15a] although somewhat below the value of 88.3 ± 0.8 kcal mol^{-1} obtained by Pedulli and co-workers[15b] in benzene solution. For the present calculations, we estimate our BDE values to be accurate to within ca. 1−2 kcal mol^{-1} of gas-phase experiments, i.e., to essentially within experimental error. For determination of the ionization potential we calculated the adiabatic ionization potential at 0 K. This value corresponds to the internal energy change $\Delta E°_0$ for ArOH (g) → $ArOH^+$ (g) + e^- (see Experimental Section for details of the calculation).

SCHEME 1[a]



[a] Reagents and conditions: (a) K_2CO_3, acetone/CH_3I; (b) tBuLi/THF, 78 °C/CH_3I; (c) $Pb(OAc)_4$/benzene, 50 °C; (d) 80% HOAc; (e) $Na_2S_2O_4$/ether/water.

Measurement of Rate Constant for Reaction with DPPH•. Kinetic measurements with DPPH• were similar to those described previously by Foti et al.,[6] except that we used the more polar DPPH• and ethyl acetate solvent instead of DOPPH• in heptane (for details, see the Experimental Section). The experiments were carried out in a stopped-flow apparatus at the National Research Council in Ottawa. The decay of DPPH• was monitored at 519 nm in the presence of varying (excess) concentrations of antioxidant at room temperature, giving the second-order reaction (eq 1):

$$\text{ArO-H} + \text{DPPH}^\bullet \rightarrow \text{ArO}^\bullet + \text{DPPH}_2 \qquad (1)$$

Under these pseudo-first-order conditions the observed rate constant k_{obs} is given by eq 2:

$$k_{obs} = k_0 + k_{DPPH}[\text{ArOH}] \qquad (2)$$

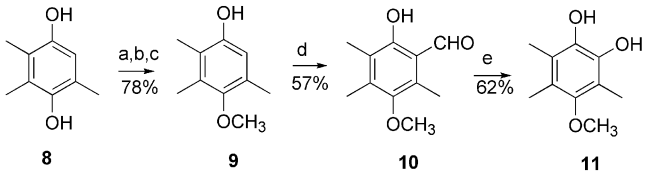
where k_0 is the intercept and the second-order rate constant k_{DPPH} is the slope of the plot of k_{obs} vs [ArOH].

Results and Discussion

A. Synthesis. The synthesis of the catechol (**2**, 3-methyl-4-methoxy-1,2-dihydroxybenzene) starting from sesamol (**3**) is outlined in Scheme 1. Deprotection of the methylendioxy group in **4** was accomplished by treatment with $Pb(OAc)_4$ in refluxing benzene, which generated the intermediate ortho ester **5**. Hydrolysis of **5** in aqueous acetic acid gave in 85% yield a mixture of the desired catechol **2** and the corresponding *o*-quinone **6** as a reddish oil, accompanied by 15% of the carbonate **7**. The red mixture, dissolved in ether, when stirred with aqueous

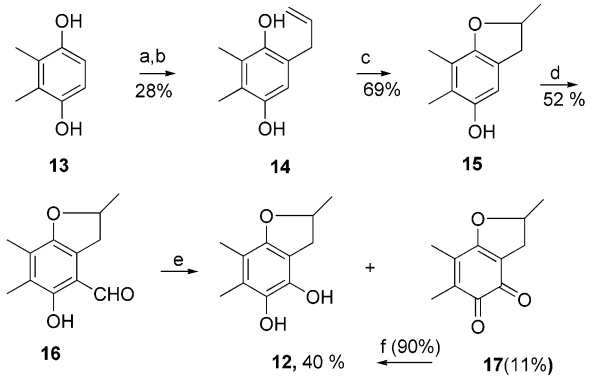
(8) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13−19.
(9) Scaiano, J. C.; Martin, A.; Yap, G. P. A.; Ingold, K. U. *Org. Lett.* **2000**, *2*, 899−901.
(10) Wright, J. S.; Chepelev, L. Unpublished results.
(11) DiLabio, G. A.; Wright, J. S. *Free Radicals Biol. Med.* **2000**, *29*, 480−485.
(12) DiLabio, G. A.; Pratt, D. A.; LoFaro, A. D.; Wright, J. S. *J. Phys. Chem. A* **1999**, *103*, 1653−1661.
(13) Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245−4252.
(14) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.
(15) (a) Wayner, D. D. M.; Lusztyk, E.; Page, D.; Ingold, K. U.; Mulder, P.; Laarhoven, L. J. J. A.; Aldrich, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 8737−8744. (b) Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063.

SCHEME 2[a]



[a] Reagents and conditions: (a) tBu(Me)$_2$SiCl/imidazole/DM; (b) K_2CO_3/acetone/CH_3l; (c) Bu4NF/CH_2Cl_2; (d) $SnCl_4$, Bu_3N; $(CH_2O)_n$, toulene, 95 °C; (e) H_2O_2/NaOH.

SCHEME 3[a]



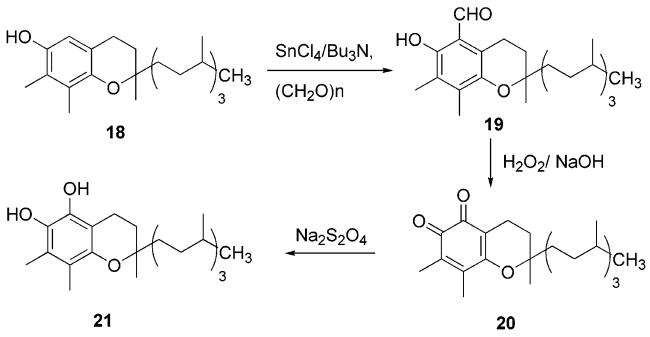
[a] Reagents and conditions: (a) allyl bromide/acetone/CH_3l/K_2CO_3; (b) decalin, 190 °C; (c) $H^{(+)}$/benzene; (d) $SnCl_4$, Bu_3N, $(CH_2O)_n$, toluene, 95 °C; (e) H_2O_2/NaOH; (f) $Na_2S_2O_4$.

sodium dithionite gave **2** as a yellowish oil in 91% yield. This oil takes on a reddish color shortly after exposure to air, indicative of possible oxidation to its *o*-quinone **6**. However, the 200-MHz proton NMR spectrum taken after several days of storage in a closed vessel continued to indicate the presence of more than 98% of the catechol structure.

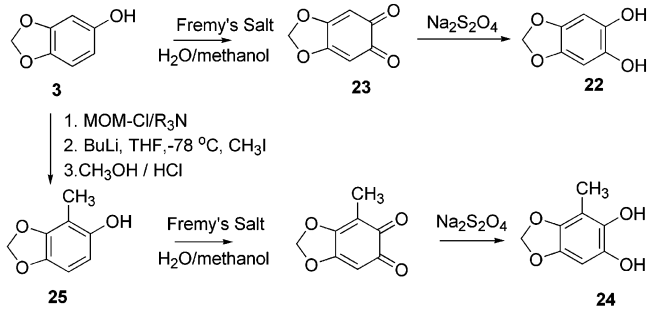
2,3,5-Trimethylhydroquinone, **8**, was chosen as the starting material for the preparation of the fully substituted monocyclic catechol **11** (Scheme 2). Protection of the less hindered OH group in **8**, methylation of the remaining phenolic group, and deprotection afforded the methoxyphenol **9** in greater than 80% overall yield. *o*-Formylation with the Vilsmaier−Hack reagent gave the salicyladeyde **10**, which upon reaction with H_2O_2/NaOH treatment yielded the desired **11**.

We decided to target the bicyclic catechol **12** since reduction of the size of the nonaromatic ring in tocophoryl analogues from the dihydropyran to dihydrofuran is known to increase the antioxidant capability.[16,17] Thus, 2,3-dimethyl-1,4-dihydroxybenzene,**13**, was monoallylated and the resultant ether was subjected to a Claisen rearrangement at 190 °C in decalin to give **14** (Scheme 3). Treatment with TsOH in refluxing benzene caused cyclization to **15**. *o*-Formylation and treatment with basic hydrogen peroxide, as in the formation of **11**, afforded a 4:1 mixture of the desired **12** and the corresponding *o*-quinone **17** in 51% yield (Scheme 3). The reddish crystalline quinone **17** was readily reduced to the nearly colorless catechol **12** upon stirring an ether solution with

SCHEME 4



SCHEME 5



aqueous sodium dithionite. The spectroscopic properties of **12** and **17** are in agreement with the assigned structure; see the Experimental Section.

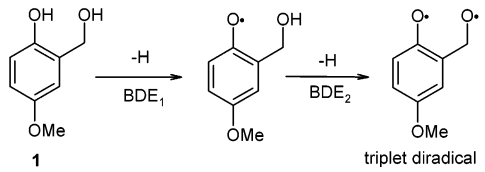
Formylation of γ-tocophorol, **18**, under the $SnCl_4$/Bu_3N/$(CH_2O)_n$ conditions afforded the fully substituted salicylaldehyde **19** in 19% yield (Scheme 4). Treatment with H_2O_2 and NaOH gave 50% of isolated *o*-quinone **20**. Reduction with aqueous sodium dithionite as before yielded the catechol **21** as an oily material that quickly turned reddish due to its ease of oxidation back to **20** (Scheme 4).

Finally, the symmetrical methylenedioxycatechol **22** was obtained by Fremy's salt oxidation of sesamol **3** to the *o*-quinone **23** followed by reduction with sodium dithionite in a two-phase ether−water system. The methylated analogue **24** was also prepared from **3** via conversion to the MOM ether, ortho-directed metalation and methylation, Fremy's salt oxidation to **25**, and finally $Na_2S_2O_4$ reduction (Scheme 5).

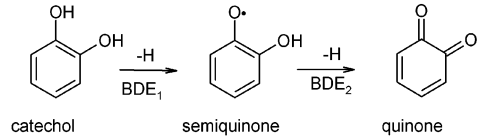
BDE, IP, and Kinetics. To study the DPPH$^\bullet$ kinetics for the various molecules tested, consider that all the compounds tested except α-tocopherol have two exchangeable hydroxyl group H-atoms, and could in principle undergo reaction with two molecules of DPPH$^\bullet$, complicating the kinetics. However, the pseudo-first order rate constants are determined by exponential fits to the decay curves near time zero and we assume that we are measuring the rate of reaction of only the first (weaker) OH abstraction, i.e., eq 1. For antioxidant activity, on the other hand, participation of the second OH group is a distinct possibility and depends on the BDE. For **1**, the two possibilities are shown in Scheme 6 below, where it is clear that the weaker bond is the phenolic OH and the stronger bond is the benzylic OH, since aliphatic alcohols have BDEs in the range 100−105 kcal mol^{-1}. In this case the final product would be a (triplet) diradical that does not have significant stabilization.

(16) Burton, G. W.; LePage, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791−7792.
(17) Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950−51.

SCHEME 6



SCHEME 7



For the catechols, on the other hand, the first oxidation leads to a semiquinone and the second to a quinone, as shown in Scheme 7. Here it is not obvious which step has the lower BDE since catechols are known to be prone to oxidation, with formation of quinones being common, even in the presence of the weak oxidant molecular oxygen.

Results of the kinetic studies are collected in Table 1. Reproducibility in the kinetic runs was excellent with very little deviation in the linear fits to the data, as shown by the high values of R^2. Values of the second-order rate constant k_{DPPH} range over more than 3 orders of magnitude, with the benzylic compound **1** being least reactive and **22** and **24** the most reactive, both of the latter being almost 2 orders of magnitude more reactive with DPPH$^\bullet$ in ethyl acetate than α-tocopherol.

The calculated BDE and IP values are also shown in Table 1. Compound **1** contains an internal H-bond that donates a hydrogen atom leaving the phenoxyl radical, shown in Figure 1. For the radical that forms (at right, Figure 1), by performing an initial conformer search we allow the OH group remaining to rotate to form a new intramolecular H-bond, i.e., the conformer search assumes that there is sufficient energy available at 298 K to make this rotation possible (the barrier is ca. 3 kcal mol^{-1}). This "free rotation in the radical" assumption is made throughout all calculations where the barriers are expected to be low, as in torsional motion about a single bond. Compound **1** has a primary BDE of 79.5 kcal mol^{-1} (for the phenolic O−H) that lies 7.8 kcal mol^{-1} below phenol, and is therefore predicted to react more slowly than α-tocopherol (expt BDE 77 kcal mol^{-1}, calcd BDE 75.0 kcal mol^{-1}), which it does. Additivity values for substituents[14] can also be used to predict the BDE; it appears that the combined effects are simply that of a *p*-methoxy group (−6 kcal mol^{-1}) and an *o*-methyl group (−2 kcal mol^{-1}) leading to the observed ΔBDE = −8 kcal mol^{-1}. A BDE for the second exchangeable OH was calculated to be above 100 kcal mol^{-1} and therefore would not participate in any exchange reaction.

Compound **2** is the least-substituted member of the catechol series. The weaker OH bond is para to the methoxy group, corresponding to BDE_1. From additivity we obtain −9 for the catechol group, −0.5 for *m*-methyl, and −6 for *p*-methoxy, giving a predicted ΔBDE = −15.5 kcal mol^{-1}, in reasonable agreement with the observed ΔBDE = −14.6 kcal mol^{-1} (using 87.10 − 72.5). The second oxidation will now produce the corressponding quinone (as in Scheme 7). Loss of the second H-atom is now competitive with the first due to the resonance stabilization in the quinone and BDE_2 being only 75.8 kcal mol^{-1}. Thus the semiquinone can be relatively easily further oxidized since its BDE_2 is comparable to the primary BDE in α-tocopherol.

Compound **11** completes the substitution of the benzene ring, and shows how use of additivity values must be tempered with caution. Simple additivity predicts that ΔBDE for the first abstraction is −9 (catechol), −2 (*o*-methyl), −1.0 (two *m*-methyl), and −6.0 (*p*-methoxy), giving a predicted BDE of 71 kcal mol^{-1} vs the calculated 73.6 kcal mol^{-1}. This exceeds our usual error from additivity values because there is a new interaction that must be considered, which has been discussed previously[14] for a similar case. Figure 2 shows the geometry of **11** prior to loss of an H-atom. The methoxy group is forced out-of-plane by almost 90°. This reduces optimal overlap of the methoxy oxygen relative to its normal position, rendering this a less electron-donating substituent; a corrected additivity value for this substituent is now only −2.6 kcal mol^{-1}, leading to a much better estimate of the effect of this functional group on the BDE. The secondary BDE is even lower at 72.6 kcal mol^{-1}, so the second oxidation (not measured) should be even more rapid than the first.

Compound **12** was designed to take advantage of the enhanced planarity of the five-membered ring, which was shown previously[16,17] to improve the activity relative to α-tocopherol. At the same time introducing the catechol functionality has been introduced and the phytyl tail truncated to a single methyl group. This compound has the very low BDE of 68.7 kcal mol^{-1}, right at the lower limit of our design window. The second BDE is also very low at only 71.7, indeed it was necessary to protect this compound from air or it rapidly autoxidized to form the red quinone (not characterized).

Compound **21** is similar to **12**. It is α-tocopherol with a catechol group replacing the *o*-methylphenol group in α-tocopherol. We refer to this molecule as "Super-E" since it closely resembles the original molecule but now has low primary and secondary BDE values of 69.3 and 70.5 kcal mol^{-1}, respectively. This compound is also prone to air oxidation. Compound **22** is similar to **21** since it lies at the lower edge of the design window with a BDE_1 value of 69.0 kcal mol^{-1}. Note that in this case the BDE_2 value falls below the window at 67.5 kcal mol^{-1}. Finally, **24** lies slightly below our design window with both BDEs at ca. 67 kcal mol^{-1}; regeneration by ascorbate will be problematic in this case. Also, at some point when the BDE is low enough the compound will become a pro-oxidant via direct reaction with oxygen, and it will be of interest to see when this behavior is reached. To study this problem in a biological context, it would be of interest to extend our calculations to include free energy changes in the presence of the appropriate concentration of oxygen, as well as solvation effects. One possible reaction is direct hydrogenation, according to ArOH + O_2 → ArO$^\bullet$ + $HO_2^\bullet$, but there are other variations including electron transfer from the corresponding anion ArO^- to oxygen to generate superoxide O_2^-; this process will depend on the p*K* of the acid.

Table 1 also shows the IP values relative to phenol. From prior work we know that α-tocopherol normally reacts by H-atom transfer and not electron transfer, i.e

TABLE 1. Rate Constant for DPPH• + Compound in Ethyl Acetate Solvent, Calculated Bond Dissociation Enthalpy of the First (BDE_1) and the Second (BDE_2) Exchangeable (OH) Hydrogen Atom, and Calculated Ionization Potential Relative to Phenol (ΔIP)

compd	k (M^{-1} s^{-1})	R^2	BDE_1 calcd (kcal mol^{-1})	BDE_2 calcd[a] (kcal mol^{-1})	ΔIP calcd[b] (kcal mol^{-1})
1	2.9	0.9942	79.5	111.0	−22.1
2	200	0.9995	72.5	75.8	−25.5
11	210	0.9993	73.6	72.6	−24.9
12	3000	0.9999	68.7	71.7	−33.7
21	4500	0.9980	69.3	70.5	−36.0
22	5040	0.9988	69.0	67.5	−28.7
24	8870	0.9984	66.9	67.3	−31.3
p-methoxyphenol	1.1	0.9987	81.0		ca. −22
α-tocopherol	160[d]	0.9992[d]	75.0[e]		−36.2

[a] BDE for loss of the second H-atom after the first has already been lost. For a catechol, BDE_2 would be the loss of an H-atom from the semiquinone radical. [b] Relative to phenol in the same basis set, for which we obtain 184.06 kcal mol^{-1}. [c] In this case BDE_2 corresponds to forming a triplet product, since quinone formation is not possible. [d] Literature value from ref 19. [e] The $C_{16}H_{33}$ (phytyl tail) was replaced by a methyl group in the calculation.

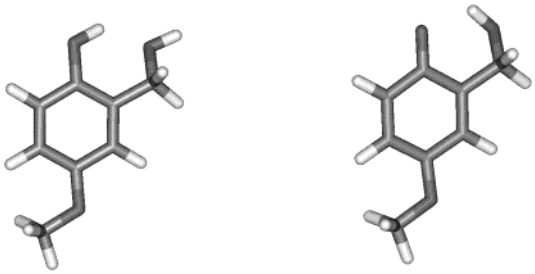


FIGURE 1. (a) Parent benzyl alcohol (structure **1**) showing starting conformation. (b) Radical formed after first H-atom abstraction, showing benzylic OH rotated toward the phenoxyl radical center.

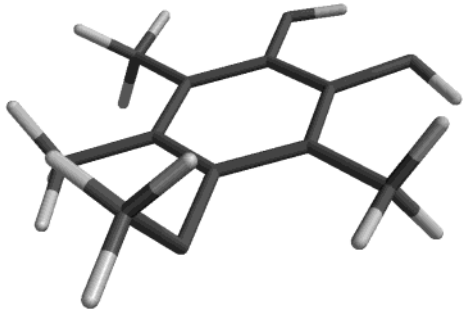


FIGURE 2. Structure of the fully substituted catechol **11**, showing that the methoxy group is rotated 90° out of plane due to interaction with adjacent methyl groups.

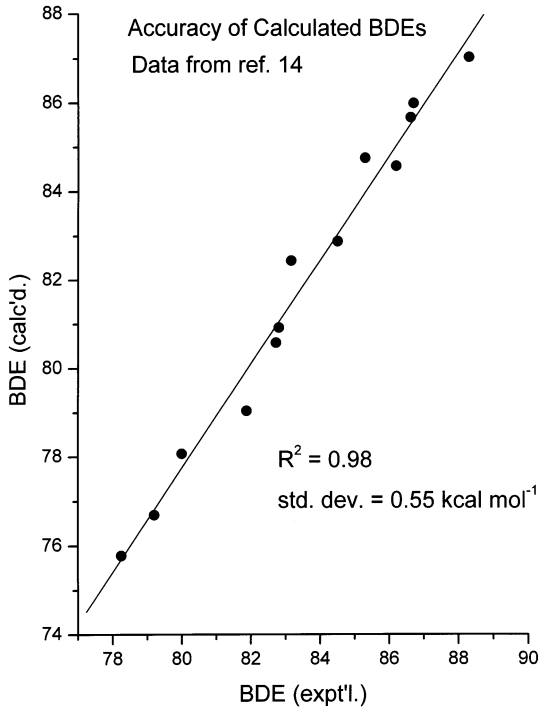


FIGURE 3. Correlation between calculated gas-phase BDEs and measured solution-phase BDEs (see ref 14 for data) for substituted phenols.

the mechanism ArOH → $[ArOH]^+ + e^-$ to form the radical cation is not observed. For α-tocopherol the IP lies 36.0 kcal mol^{-1} below phenol in our calculation. Other compounds such as aromatic amines which are prone to formation of radical cations in solution have ΔIP values at least 40 kcal mol^{-1} below those of phenol.[14] Since none of the compounds in Table 1 are more easily ionized than α-tocopherol, we do not expect them to react by an electron-transfer mechanism.

Accuracy of BDE and IP Calculations. In ref 14 and elsewhere we have discussed the accuracy of the calculated BDE data using the (RO)B3LYP/6-311+G(2d,-2p)//AM1/AM1 method. Our BDE calculations for phenol and substituted phenols can be compared to accurate solution-phase (benzene) values obtained by Pedulli and co-workers.[15b] Allowing for a slight shift due to the change from gas to benzene solution, and for the use of locally dense instead of full basis sets, there should nevertheless be a good correlation between gas- and solution-phase BDEs. In Figure 3 we have plotted the BDE (calculated, gas) vs BDE (experimental, benzene) for a set of 13 substituted phenols, omitting only the *o*,*o*-di-*tert*-butylphenol case for which the B3LYP functional fails.[14] Given that the experimental errors are between 0.12 and 0.8 kcal mol^{-1} for this data set and that the data span a range over 10 kcal mol^{-1} with a standard deviation of only ca. 0.5 kcal mol^{-1}, it can be seen that the theoretical calculation compares well with this highly precise set of experimental measurements. In extending the calculation to more complex substituted phenols it is hard to be absolutely sure that there are no anomalies, but we believe from this and other examples that the calculated Δ*B*DEs are accurate to within ca. 1.0 kcal mol^{-1}.

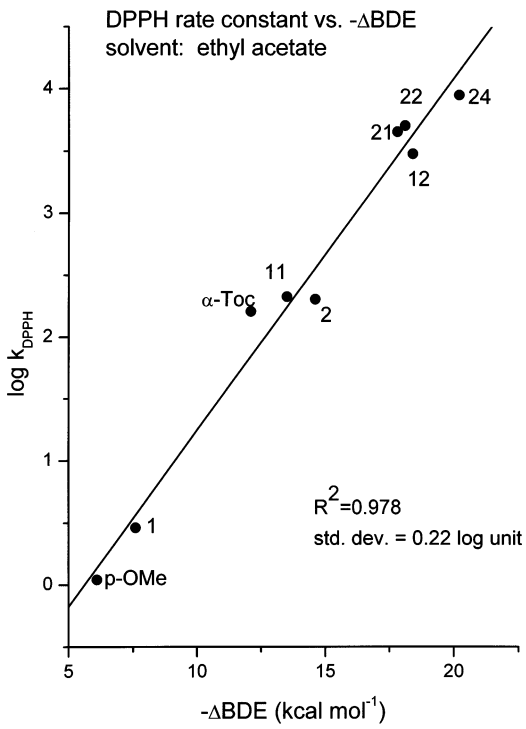


FIGURE 4. Plot of log k_{DPPH} vs change in BDE relative to phenol (87.1 kcal mol^{-1}). The ΔBDE axis has reversed sign, e.g. *p*-methoxyphenol has BDE = −6.1 kcal mol^{-1}, log k_{DPPH} = 1.1 M^{-1} s^{-1}.

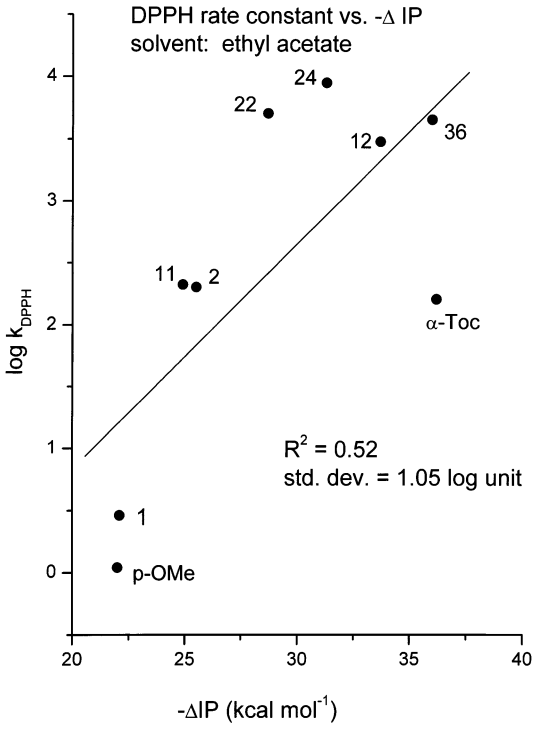


FIGURE 5. Plot of log k_{DPPH} vs change in IP relative to phenol. The ΔIP axis has reversed sign (see Table 1).

The IP calculations were monitored in an extensive series of comparisons on phenol with a variety of electron-donating and electron-withdrawing substituents. By using the method described below, values of the IP relative to phenol with the same method of calculation are expected to provide a set of ΔIP values accurate to ca. 2 kcal mol^{-1}.

Correlation between DPPH• Kinetics and BDE. Results from the present experiment are shown in Figure 4. The data now extend over nearly 4 orders of magnitude in k_{DPPH} and thus provide a stringent test of using BDEs to correlate rate data. There is a very good linear correlation between log k_{DPPH} and ΔBDE , with the R^2 value being 0.978 for nine data points. This correlation includes an additional value we determined for *p*-methoxyphenol (see Table 1), which allowed us to extend the correlation over a wider range in BDE. The slope in ethyl acetate is somewhat less than that for the Foti correlation in heptane,[6] being 0.284 log unit per kcal mol^{-1} in BDE, whereas Foti et al. obtained 0.352 log unit per kcal mol^{-1} in BDE. Note that the rates are also much lower in ethyl acetate than in heptane due to hindering of the H-atom abstraction by H-bonding in the more polar solvent.[18] An example that relates the two series of data is *p*-methoxyphenol, which has a rate constant of 240 in heptane but only 1.1 in ethyl acetate.

The quality of the correlations between the present data and the Foti data, which span a somewhat wider range in BDE (ca. 30 kcal mol^{-1}), is also similar. The molecules containing the lowest BDEs in the present paper are comparable to the most reactive molecules described by Foti et al., e.g. their 4-methoxy 1,8-naphthalene diol, which had a calculated BDE value of 67.5 kcal mol^{-1}, very close to our compound **24** with BDE = 66.9 kcal mol^{-1}. Foti et al.[6] also looked at kinetics of reactions with peroxyl radicals and obtained a good linear correlation with BDE values; this adds confidence that tests with the nitrogen radical DPPH• will mimic behavior in systems which contain peroxyl radicals ROO•. The latter are generated biologically via normal metabolism and are known to play a role in lipid peroxidation[1].

Correlation between DPPH• Kinetics and IP. As described above, we believe that the kinetics of reaction between DPPH• radicals and the catechols in ethyl acetate should proceed by H-atom transfer rather than by single-electron transfer to form the radical cation, i.e., the reaction DPPH• + ArOH → DPPH$_2$ + [ArOH]$^+$. Since the radical cation [ArOH]$^+$ rapidly equilibrates to lose a proton and generate the phenoxyl radical, it can be difficult to distinguish between the hydrogen-atom and single electron-transfer mechanisms. One instructive approach to try to distinguish between mechanisms is to plot the ionization potential relative to phenol, ΔIP, vs log k_{DPPH} and examine the quality of the correlation. This graph is shown in Figure 5. It is clear from the large scatter that the BDE shows by far the better correlation than the IP (e.g. R^2 values of 0.98 or 0.52 for BDE and IP, respectively), consistent with our argument that the reaction proceeds by H-atom transfer.

It should be noted that these conclusions apply to the relatively nonpolar solvent ethyl acetate, in which the DPPH measurements were made in this paper. In water, one would have to examine whether the mechanism may involve electron transfer from an anion, that originating

(18) Valgimigli, L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 9966−9971.

from either DPPH or from the catechols,[24] which have p*K* values near 10. It is generally the case that when an *anionic* form is present, as in the case of ascorbate where at physiological pH 7.4 the ascorbate anion is predominant, then we expect electron transfer to be the most important mechanism of reduction of a free radical. Even in that extreme case, however, H-atom transfer is a competing mechanism and cannot be disregarded.

Catechol Toxicity. Catechols are known to exert toxic effects in cells, mainly via two mechanisms.[22] In the first, they become oxidized to quinones which then act as Michael acceptors. The nucleophiles may be proteins, DNA, or glutathione (especially as the glutathione anion GS^-). Glutathione depletion in particular leads to a change in the redox environment of the cell, generally with negative consequences.[23] In the second mechanism, the quinones are reduced to semiquinones by reducing agents or enzymes in the cell. These semiquinones then redox cycle to the quinone and back to semiquinone, reducing oxygen to superoxide in the process, and hence the system acts as a free radical generator. This mechanism can lead to oxidative stress in cells, causing lipid peroxidation or other oxidative damage.

The rate of reaction of quinones as Michael acceptors is variable. It depends on whether the β-carbon position is unhindered sterically, and also whether the ring contains electron donors near the β-carbon. The latter effect reduces the electrophilicity of the carbon under attack and may prevent reaction altogether. Of the compounds we have described only **2** should be a strong Michael acceptor. The remainder are either hindered sterically or have strong electron donors at this position, and hence should be relatively unreactive.

The question of redox cycling and the "tuning" of the catecholic antioxidants to retard the rate of reaction with molecular oxygen remains an open question, which also relates to when an antioxidant becomes a pro-oxidant. In general the catechols are thought to act as an antioxidant by transfer of the first H-atom to a free radical (BDE_1, Table 1) but as a pro-oxidant by transfer of a second H-atom from the semiquinone (BDE_2, Table 1) with subsequent redox cycling between quinone and semiquinone and the resulting creation of oxidative stress via generation of superoxide ion.[1] On the other hand, Table 1 shows that the catechols in this paper are generally comparable in BDE_1 and BDE_2, in fact in most cases $BDE_2 > BDE_1$, suggesting that these compounds should not be particularly active at redox cycling. In menadiol, by comparison, whose corresponding quinone is thought to induce oxidative stress by redox cycling, we have calculated[10] that the second BDE is much lower than the first, consistent with the observed toxicity. Note, however, that menadione also has an open ring position that can undergo nucleophilic attack, so toxicity can also result from glutathione depletion and the changing redox status of the cell.

Conclusions

In this paper we discussed a design strategy to create antioxidants which could be potentially useful for biological purposes, and decided on a "design window" in the range 68−75 kcal mol^{-1}. On the basis of this strategy we examined a series of target compounds containing a weak O−H bond, with most of the molecules within the design window and some outside it. We report the synthesis of seven novel compounds, including a benzylic phenol and six catechols. BDE values were calculated for loss of the first and second H-atom in these compounds by using density functional techniques with the B3LYP functional, as well as ionization potentials, and we believe these calculations to be accurate to within ca. 2 kcal mol^{-1}. Primary BDE values were in the range 67−81 kcal mol^{-1}, with secondary BDEs ranging from 67.5 to >100 kcal mol^{-1}. The compounds were then tested for reactivity with the free radical DPPH$^\bullet$. A very good linear correlation was obtained between log $k_{DPPH^\bullet}$ and the BDE, showing that the BDE can be used to predict reactivity in this series. On the other hand, a poor correlation was obtained between log $k_{DPPH^\bullet}$ and the IP, showing that the ionization mechanism is not active in this reaction, which was carried out in ethyl acetate. Aspects of catechol toxicity were discussed, which are relevant to biological experiments. Because of the high reactivity with DPPH$^\bullet$ the compounds are potentially interesting in biological applications, and a testing program is now under way to determine toxicity and protective effects in cell cultures using these novel synthetic antioxidants.

Experimental Section

Calculation of BDE. For the calculation of the BDE according to the LLM method, we used the AM1 semiempirical method to obtain the optimized geometry and frequencies of parent and radical (BDE_1), or radical and quinone (BDE_2), where $T = 298.15$ K, $P = 1.00$ atm, and the AM1 frequencies are scaled by the factor 0.973. At the geometry minimum a single-point calculation was done with (RO)B3LYP/6-311+G-(2d,2p), where RO indicates that for the radical the restricted open-shell B3LYP method was used. All electronic energies are then corrected by the thermal contribution to the enthalpy to obtain $H°_{298}$, the standard gas-phase enthalpy at 298 K. To complete the specification of the method, we set the electronic energy of the H-atom to its exact value of −0.50000 hartree, and obtain its enthalpy $H°_{298} = -0.50000 + {}^5/_2RT = -0.49764$ hartree. Starting geometries were generally obtained with the PC-Spartan[20] builder module, using AM1; coordinates were then sent to the Gaussian 98 program[21] for all subsequent calculations.

Calculation of IP. IPs are only reported for parent hydrocarbons (i.e. the first ionization) and not for the radicals which can form in the catechols. Geometries and frequencies were calculated and scaled with use of AM1 as above. To obtain

(19) Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem*. **1999**, *64*, 3381−3383.
(20) Spartan '02 for Windows, Wavefunction, Inc.: Irvine, CA, 2002.
(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7, Gaussian, Inc., Pittsburgh PA, 1998.
(22) Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J. *Chem. Res. Toxicol.* **2000**, *13*, 135−160.
(23) Nelson, S. D.; Pearson, P. G. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *30*, 169−195.
(24) K. U. Ingold, personal communication.

the adiabatic ionization potential we took the optimized geometry for parent and (radical) cation and performed a (RO)-B3LYP/6-31G(d) calculation, as described in ref 25. The difference between parent and cation at 0 K corresponds to $\Delta E°_0$ for ArOH (g) → $[ArOH]^+$ (g) + e^-. Reported values are relative to the calculated value for phenol, for which we obtain $\Delta E°_0 = 184.06$ kcal mol^{-1}. This lies well below the experimental value (see ref 25 for an extensive list of experimental data) of 196.2 ± 0.02 kcal mol^{-1}; however, we found previously[25] that there is a systematic error arising from the treatment of the benzene ring, and that use of ΔIP values for substituted phenols caused a large error cancellation, resulting in ΔIP values accurate to ca. 2 kcal mol^{-1}.

DPPH• Kinetics. The stopped-flow apparatus is an Applied Photophysics SX 18 MV spectrometer with a xenon 150 arc light source. DPPH• was obtained from Northern Sources, Inc., and was used without further purification. All compounds were dissolved in ether, washed with aqueous sodium dithionite, and then re-isolated prior to the kinetic measurements. In a typical run, DPPH• (ca. 5×10^{-5} M) was deoxygenated under nitrogen, and then mixed 1:1 with (deoxygenated) solutions of antioxidants, where the antioxidant ArOH concentration was usually 2 orders of magnitude greater, so as to obtain pseudo-first-order rate constants. The decay of DPPH• was monitored at 519 nm in the presence of a given (large excess) concentration of antioxidant at room temperature. Under these conditions the decay curve is pseudo-first order, and it was well fitted by a single-exponential function $[DPPH] = [DPPH]_0 \exp(-k_{obs}t)$ + constant. From plots of k_{obs} vs [ArOH] at five concentrations the second-order rate constant was obtained as the slope of the plot.

Syntheses: 2-Hydroxymethyl-4-methoxyphenol (1). A solution of 2-hydroxy-5-methoxybenzaldehyde (1.00 g, 66 mmol) and sodium borohydride (0.201 g, 53 mmol) in 30 mL of THF was stirred for 3 h at 0 °C. Aqueous sodium hydroxide (10%, 10 mL) was added and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic portions were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by gradient flash chromatography (30 g of silica gel, ethyl acetate−hexane eluent, 5% polarity increase) to afford 0.671 g, 66% of **1** as a white solid: mp 77−79 °C.

4-Methoxybenzo[1,3]dioxole. Anhydrous potassium carbonate (35.0 g, 0.253 mol) was added to the solution of sesamol, **3** (5.01 g, 36 mmol), in 80 mL of acetone at room temperature under a nitrogen atmosphere. The mixture was stirred vigorously for 1 h. Methyl iodide (24.8 mL, 40 mmol) was added dropwise and the reaction mixture was refluxed at 55 °C for 42 h. The resulting slurry was filtered through Celite and the filtrate evaporated in vacuo. The residue was taken up in 40 mL of water and extracted with ether (3 × 30 mL). The combined ether fractions were washed with 25 mL of 10% sodium hydroxide solution, followed by 2 × 25 mL of water, dried, filtered and concentrated in vacuo to afford anisole (4.61 g, 84%) of 5 methoxybenzo[1,3]dioxole as a yellow liquid. This material was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.73 (s, 3H, methoxy), 5.89 (s, 2H, methylene dioxy), 6.31 (dd, J = 8.5, 2.6 Hz, 1H, H-6), 6.47 (d, J = 2.6 Hz, 1H, H-4), 6.69 (d, J = 8.5 Hz, 1H, H-7); MS [EI, m/z (%)] 152 [MH^+] (100), 137 (74), 107 (32), 79 (31), 51 (17); HRMS calcd for $C_8H_8O_3$ 152.0473, found 152.0477.

5-Methoxy-4-methylbenzo[1,3]dioxole (4). A 1.7 M solution of *tert*-butyllithium in pentane (27.0 mL, 0.046 mmol) was added dropwise to a solution of 5-methoxybenzo[1,3]dioxole (4.60 g, 30 mmol) in dry THF (20 mL), under nitrogen at 0 °C. The mixture was stirred for 30 min and methyl iodide (3.80 mL, 61 mmol) was added dropwise. The reaction mixture was kept at 0 °C for 1 h and an additional 2 h at rt. Workup involved quenching with saturated ammonium chloride solution (10 mL), extraction with ethyl acetate (3 × 20 mL), and drying and evaporating the organic extracts. The crude product, 5.29 g of brown oil, was purified via gradient flash chromatography (125 g of silica gel, hexanes−ethyl acetate eluent, polarity increase by 5%). The yield of **4**, a white solid (mp 39−41 °C), was 3.60 g (72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H, methyl), 3.76 (s, 3H, methoxy), 5.89 (s, 2H, methylenedioxy), 6.25 (d, J = 8.4 Hz, 1H, H-6), 6.58 (d, J = 8.4 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 153.88 (C-5), 147.07 (C-3), 141.42 (C-1), 109.67 (C-4), 104.62 (C-7), 102.12 (C-6), 101.24 (C-2), 56.46 (methoxy), 9.13 (methyl); MS [EI, m/z (%)] 166 [MH^+] (98), 151 (100), 121 (47), 93 (16), 65 (17); HRMS calcd for $C_9H_{10}O_3$ 166.0630, found 166.0626.

Acetic Acid 5-Methoxy-4-methylbenzo[1,3]dioxol-2-yl Ester (5). Lead tetraacetate (14.4 g, 32.5 mmol), recrystallized from glacial acetic acid, was added to a solution of 5-methoxy-4-methylbenzo[1,3]dioxole (**4**, 3.60 g, 21.7 mmol) in benzene (60 mL), under nitrogen, and stirred at reflux (75−80 °C) for 20 h. The reaction mixture was cooled, diluted with 30 mL of water, and extracted with ether (3 × 25 mL). The combined organic extracts were dried over Mg_2SO_4, filtered, and concentrated in vacuo to afford a brown oil (4.48 g, 92% crude). This material was reacted as described below without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H, acetate methyl), 2.12 (s, 3H, methyl), 3.77 (s, 3H, methoxy), 6.36 (d, J = 8.0 Hz, 1H, H-6), 6.70 (d, J = 8.0 Hz, 1H, H-7), 7.64 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.16 (acetate −C═O), 151.51, 146.55, 142.79, 113.96, 108.76, 103.14, 102.10, 56.79 (methoxy), 22.32, 9.09 (methyl).

3-Methyl-4-methoxy-1,2-benzoquinone (6), 3-Methyl-4-methoxy-1.2-dihydroxybenzene (2), and 5-Methoxy-4-methylbenzo[1,3]dioxol-2-one (7). Crude acetate from above (4.48 g, 20 mmol) was dissolved in 80% aq acetic acid (100 mL) and stirred at room temperature for 48 h. The solvent was evaporated and the remaining residue washed with toluene (4 × 1 mL) and condensed to dryness in vacuo. Gradient flash chromatography (125 g silica gel, hexanes−ethyl acetate eluent with 5% polarity increase) afforded a mixture of **2** and **6** (2.62 g, 85%) as a red liquid and **7** (0.540 g, 15%) as an off-white solid: mp 110−111 °C. For **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H, methyl), 3.80 (s, 3H, methoxy), 6.59 (d, J = 8.8 Hz, 1H, H-6), 6.93 (d, J = 8.8 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 155.5 (C-2), 152.3 (C-5), 143.0 (C-1), 137.3 (C-3), 111.3 (C-4), 107.1 (C-7), 105.7 (C-6), 56.6 (methoxy), 9.2 (methyl); MS [EI, m/z (%)] 180 [MH^+] (100), 135 (12), 121 (84), 93 (44), 65 (17); HRMS calcd for $C_9H_8O_4$ 180.0422, found 180.0392.

3-Methyl-4-methoxy-1,2-dihydroxybenzene (2). A solution of sodium dithionite (20.75 g, 11.9 mmol) in 75 mL of water was added to a rapidly stirred solution (2.62 g, 17.2 mmol) of the o-quinone **6**/catechol **2** mixture from above in 25 mL of ether. The color of the reaction mixture changed from orange to bright yellow within 3 min. Aqueous 10% hydrochloric acid (10 mL) was added and the reaction mixture was extracted with ether (4 × 20 mL). The combined ether extracts were washed with saturated sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated to give **2** (2.39 g, 91%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H, methyl), 3.74 (s, 3H, methoxy), 5.83 (br s, 2H, hydroxyl), 6.28 (d, J = 8.7 Hz, 1H, H-5), 6.60 (d, J = 8.7 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 152.8 (C-4), 143.5 (C-1), 137.7 (C-2), 114.2 (C-3), 112.4 (C-6), 103.0 (C-5), 56.7 (methoxy), 8.9 (methyl); MS [EI, m/z (%)] 154 [MH^+] (91), 139 (100), 121 (38), 93 (15), 65 (22); HRMS calcd for $C_8H_{10}O_3$ 154.0630, found 154.0612.

4-*tert*-Butyldimethylsilyloxy-2,3,5-trimethylphenol. *tert*-Butyldimethylsilyl chloride (1.19 g, 1.2 mol equiv) in dry DMF (5 mL) was added to a solution of 2,3,5-trimethylhydroquinone (**8**, 1.0 g, 1.0 mol) and imidazole (1.79 g, 4.0 mol equiv) in dry DMF (10 mL) at −20 °C under nitrogen. The reaction mixture was warmed to 20 °C and stirred for 2 h, poured into water, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic

(25) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *Chem. Phys. Lett.* **1999**, *311*, 215−220.

layers were washed with water (2 × 20 mL) and dried ($MgSO_4$) and the solvent was removed under vacuo. The crude product was subjected to a flash chromatography with use of ethyl acetate and hexane to give the title compound as a solid (1.5 g, 85%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.23 (s, 6H), 1.07 (s, 9H), 2.16 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 4.46 (s, 1H), 4.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.9, 143.5, 125.9, 123.8, 120.5, 118.1, 25.9, 18.3, 16.1, 13.0, 12.4, −4.2; HRMS calcd for $C_{15}H_{26}O_2Si$ 266.1702, found 266.1703.

4-*tert*-Butyldimethylsilyloxy-1-methoxy-2,3,5-trimethylbenzene. A mixture of the above phenol (0.76 g, 1.0 mol equiv), methyl iodide (0.9 mL, 5.0 mol equiv), and potassium carbonate (0.79 g, 2.0 mol equiv) in 10 mL of acetone was refluxed for 24 h. The solvent was evaporated and water (20 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate (3 × 20 mL). Flash chromatography (ethyl acetate−hexane eluent) of the crude product yielded 0.76 g (95%) of the desired product as a yellow oil. ^{1}H NMR ($CDCl_3$, 50 MHz) δ 0.18 (s, 6H), 1.00 (s, 9H), 2.08 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 3.63 (s, 3H), 6.42 (s, 1H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 150.8, 149.2, 130.4, 127.7, 125.8, 118.1, 60.0, 25.8, 18.2, 16.0, 12.8, −4.3; HRMS calcd for $C_{16}H_{28}O_2Si$ 280.1860, found 280.1859.

4-Methoxy-2,3,5-trimethylphenol (9). A solution of the above silylated phenol (0.8 g, 1.0 mol equiv) in dry THF (8 mL) was treated with Bu_4NF (4.27 mL, 1.0 M, 1.5 mol equiv) at room temperature under nitrogen for 1 h. The reaction mixture was quenched with 10 mL of water, extracted with ethyl acetate, and processed in the usual manner. Flash chromatography of the crude product [ethyl acetate and hexane] gave the pure **9** (0.45 g, 96%). ^{1}H NMR ($CDCl_3$, 50 MHz) : 2.11 (s, 3H), 2.19 (s, 6H), 3.65 (s, 3H), 4.98 (br s, 1H), 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.1, 149.7, 130.6, 128.2, 121.3, 114.5, 60.2, 15.9, 12.7, 11.9; HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996.

2-Hydroxy-5-methoxy-3,4,6-trimethylbenzaldehyde (10). The same formylation procedure as for the preparation of **16** (with **15** as a substrate) gave 57% of **10** as a yellow solid. ^{1}H NMR ($CDCl_3$, 50 MHz) δ 2.07 (s, 3H), 2.20 (s, 3H), 2.44 (s, 3H), 3.58 (s, 3H), 10.14 (s, 1H), 12.13 (s, 1H); ^{13}C NMR($CDCl_3$, 200 MHz) δ 194.5, 157.8, 148.9, 141.7, 129.9, 123.8, 116.1, 60.5, 13.7, 10.9, 10.1; HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0953.

4-Methoxy-3,4,6-trimethylbenzene-1,2-diol (11). The same procedure as for the preparation of **12** (with **16** as a substrate) gave **11** (62%) as a pinkish solid: mp 114−115 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.13 (s, 6H), 2.16 (s, 3H), 3.62 (s, 3H), 4.81 (s, 1H), 4.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 150.2, 140.0, 138.1, 121.3, 120.5, 114.4, 60.4, 12.0, 11.9, 8.9; HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0943.

4-Allyloxy-2,3-dimethylphenol and 1,4-Bis-allyloxy-2,3-dimethylbenzene. Allyl bromide (0.94 mL, 11 mmol) and potassium carbonate (2.02 g, 14.6 mmol) were added to a solution of 2,3-dimethylhydroxyhydroquinone (1.0 g, 7.3 mmol) in acetone (10 mL). The resulting mixture was stirred at reflux for 18 h, the solvent was removed in vacuo, and the remaining residue was taken up in water and extracted with ether (3 × 30 mL). Further workup followed by flash chromatography of the crude product with ethyl acetate and hexane gave two products: the desired monoallyl ether (0.45 g, 35%) as a brown semisolid and diallyl ether (0.79 g, 50%) as a yellow oil: For the monoallyl ether: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 2.20 (s, 3H), 4.46 (dt, J = 5.2, 1.6 Hz, 2H), 5.02 (br s, 1H), 5.23 (br dd, J = 10.4, 1.6 Hz, 1H), 5.46 (br dd, J = 17.2, 1.6 Hz, 1H), 6.07 (m, 1H), 6.55 (d, J = 9.0 Hz, 1H), 6.61 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.7, 147.8, 134.0, 127.4, 124.3, 116.9, 112.0, 110.7, 70.2, 12.3, 12.2; HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994:

6-Allyl-2,3-dimethylbenzene-1,4-diol (14). A solution of allyl ether (1.0 g) in 10 mL of Decalin was heated to 190−195 °C for 5 h, using the oil bath, and then cooled to room temperature. A solid product was separated by filtration and washed with hexane (20 mL). The yield of **14**, a white solid (mp 124−126 °C), was 0.81 g (81%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.14 (s, 3H), 2.16 (s, 3H), 3.31 (br d, J = 6.2 Hz, 2H), 4.44 (s, 1H), 4.61 (s, 1H), 5.15 (m, 2H), 5.97 (m, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.1, 146.2, 136.4, 124.7, 122.5, 122.0, 116.5, 116.0, 113.7, 112.5, 35.5, 12.2, 11.9; HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994.

2,6,7-Trimethyl-2,3-dihydrobenzofuran-5-ol (15). *p*-Toluenesulfonic acid (3.5 g) was added to a solution of 5-allyl-2,3-dimethylbenzene-1,4-diol **14** (3.0 g, 16.8 mmol) in benzene (40 mL) and the reaction mixture was refluxed for 8 h and then cooled to room temperature. Workup involved addition of saturated $NaHCO_3$ (20 mL), extraction with ethyl acetate (3 × 20 mL), drying ($MgSO_4$), and evaporating the solvents. The solution was filtered and condensed in vacuo to give a solid. Flash chromatography of the crude product with ethyl acetate−hexane eluent afforded **15** (2.1 g, 69%) as a white solid: mp (126−128 °C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (d, J = 6.2 Hz, 3H), 2.11 (s, 3H), 2.13 (s, 3H), 2.74 (dd, J = 14.4, 7.0 Hz, 1H), 3.21 (dd, J = 15.0, 8.8 Hz, 1H), 4.33 (s, 1H), 4.82 (m, 1H), 6.49 (s, 1H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 152.1, 147.2, 123.5, 121.9, 118.9, of 109.1, 78.9, 37.8, 21.7, 12.3, 11.8; HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994.

5-Hydroxy-2,6,7-trimethyl-2,3-dihydrobenzofuran-4-carbaldehyde (16). A solution of hydroxybenzofuran **15** (3.5 g, 19.6 mmol), tin tetrachloride (0.28 mL, 0.12 mol equiv), and tributylamine (1.87 mL, 0.4 mol equiv) in 40 mL of anhydrous toluene in a three-neck flask was stirred at room temperature for 20 min and then paraformaldehyde (1.3 g, 2.2 mol equiv) was added. The resulting yellowish solution was heated for 2 h at 90−95 °C, cooled to room temperature, poured into water (50 mL), acidified to pH 2 with 2 N HCl, and extracted with ether (3 × 50 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and filtered and the solvent was removed in vacuo. The crude residue was purified by flash chromatography with ethyl acetate and hexane to give a bright yellow solid **16** (2.1 g, 52%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47 (d, J = 6.2 Hz, 3H), 2.09 (s, 3H), 2.15 (s, 3H), 2.98 (dd, J = 15.8, 8.0 Hz, 1H), 3.51 (dd, J = 15.6, 8.6 Hz, 1H), 4.91 (m, 1H), 9.84 (s, 1H), 11.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 173.9, 154.3, 151.3, 133.4, 130.2, 124.1, 114.2, 79.3, 35.5, 21.7, 13.3, 10.7; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0943.

2,6,7-Trimethyl-2,3-dihydro-benzofuran-4,5-dione (11) and 2,6,7-Trimethyl-2,3-dihydrobenzofuran-4,5-diol (12). Hydrogen peroxide (0.2 mL, 30%) was added to a rapidly stirred solution of aldehyde **16** (1.0 g, 4.9 mmol) and sodium hydroxide (0.19 g, 1.0 mol equiv) in 16 mL of water−THF (9:1) solvent mixture, under nitrogen, at 28−30 °C. Aqueous 10% HCl was added after the solution had been stirred for 30 min at that temperature followed by 30 min at room temperature. The reaction mixture was extracted with ethyl acetate (3 × 30 mL). Further usual workup gave a crude product that consisted mainly of the desired catechol **12** and the related quinone **17**. Flash chromatography with ethyl acetate and hexane as eluent gave **17** (0.1 g, 11%) as a deep red liquid and the diol **12** (0.38 g, 40%) as a pink solid. For **17**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, J = 6.4 Hz, 3H), 1.89 (s, 3H), 2.00 (s, 3H), 2.54 (dd, J = 15.0, 7.2 Hz, 1H), 3.09 (dd, J = 15.0, 10.0 Hz, 1H), 5.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 182.3, 174.6, 171.6, 137.0, 136.8, 111.7, 84.0, 33.0, 21.9, 13.4, 11.8; HRMS calcd for $C_{11}H_{12}O_3$ 192.0787, found 192.0789. For **12**: mp 140−142 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.35 (d, J = 6.2 Hz, 3H), 1.96 (s, 3H), 2.07 (s, 3H), 2.67 (dd, J = 15.0, 6.8 Hz, 1H), 3.22 (dd, J = 15.0, 8.4 Hz, 1H), 4.76 (m, 1H), 6.50 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 152.5, 140.5, 137.5, 123.4, 110.2, 108.9, 79.4, 35.9, 22.0, 12.2, 11.8; HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0943.

2,6,7-Trimethyl-2,3-dihydrobenzofuran-4,5-diol (12). A solution of sodium dithionite (0.53 g, 6.5 mol equiv) in water (2 mL) was added in one portion to a stirred solution of the *o*-quinone **17** (0.09 g, 0.47 mmol in 4 mL of ether). The red

color of the quinone was discharged after 3 min. Aqueous hydrochloric acid (10%) was added and the opaque mixture extracted with ether (3 × 15 mL). The combined extracts were washed with saturated sodium bicarbonate (2 × 10 mL), dried over $MgSO_4$, and filtered. Evaporation of the solvent afforded the catechol **12** (0.08 g, 90%) as a yellow solid.

6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-5-carbaldehyde (19). The formylation of γ-tocopherol, **18**, was carried out with the same procedure as was the conversion of **15** to **16** above. The product **19** was obtained as a yellow oil (19% yield) following column chromatography. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (m, 12H), 0.96−1.60 (m, 24H), 1.81 (m, 2H), 2.13 (s, 3H), 2.16 (s, 3H), 3.00 (t, J = 6.8 Hz, 2H), 10.16 (s, 1H), 12.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 193.9, 155.8, 143.9, 138.3, 124.1, 117.4, 114.4, 75.0, 39.5, 39.3, 37.3, 37.2, 32.7, 32.6, 30.7, 27.9, 24.8, 24.4, 23.6, 22.7, 22.6, 20.9, 19.7, 19.6, 18.4, 13.1, 11.0; HRMS calcd for $C_{29}H_{48}O_3$ 444.3604, found 444.3605.

2,7,8-Trimethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromene-5,6-dione (20) and 2,7,8-Trimethyl-2-(4,8,-12-trimethyltridecyl)-3,4-dihydro-2*H*-chromene-5,6-diol (21). The rearrangement of **19** to **21** and **20** was carried out with the same procedure as was the conversion of **16** to **12**, above, and gave **20** (12%) as a deep red oil and **21** (50%) as a yellow oil. For **20**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81−0.84 (m, 12H), 1.00−1.41 (m, 21H), 1.49 (s, 1H), 1.59 (m, 2H), 1.72 (m, 2H), 1.92 (s, 3H), 2.00 (s, 3H), 2.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.8, 177.8, 163.2, 143.6, 134.1, 110.2, 81.3, 39.9, 39.3, 37.4, 37.3, 37.2, 37.2, 32.9, 32.7, 32.6, 32.5, 29.7, 29.1, 27.9, 25.6, 24.7, 24.4, 23.8, 22.6, 22.5, 21.3, 20.8, 19.7, 19.5, 15.3, 13.6, 11.5; HRMS calcd for $C_{28}H_{46}O_3$ 430.3449, found 430.3447. For **21**: ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.85−0.89 (m, 12H), 1.11−1.60 (m, 24H), 1.73 (m, 2H), 2.00 (s, 3H), 2.11 (s, 3H), 2.64 (m, 2H), 6.56 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (acetone-d_6, 200 MHz) δ 145.9, 141.7, 136.0, 122.9, 115.3, 107.1, 75.3, 40.4, 40.1, 33.5, 33.4, 31.7, 30.6, 30.2, 29.8, 29.4, 29.1, 28.6, 25.5, 25.1, 24.2, 23.0, 22.9, 21.6, 20.1, 17.9, 12.4, 11.5; HRMS calcd for $C_{28}H_{48}O_3$ 432.3605, found 432.3603.

Reduction of 2,7,8-Trimethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromene-5,6-dione (20) to 2,7,8-Trimethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromene-5,6-diol (21). Sodium dithionite reduction of **20** in the two-phase system ether−water was carried out as in the case of **16** to **12**. The product **21**, obtained in 89% yield, had spectroscopic properties identical with **21**, above.

Benzo[1,3]dioxole-5,6-diol (22). Sesamol (**3**, 1.52 g, 24 mmol) in 30 mL of methanol was added to a rapidly stirred solution of Fremy's salt (7.96 g, 30 mmol) and 5.49 g (40 mmol) of potassium dihydrogen orthophosphate in 400 mL of water (400 mL) at 5 °C. The color of the solution changed from light brown to bright yellow within 5 min. After 30 min the quinone **23** was extracted with 4 × 40 mL of ethyl acetate. The ethyl acetate solution was treated with a solution of sodium dithionite (9.0 g, 52 mmol) in water (30 mL) and after 5 min the yellow color changed to a colorless solution. The organic layer was acidified with hydrochloric acid (1 N), extracted with ethyl acetate (3 × 30 mL), washed with water (20 mL), dried ($MgSO_4$), and evaporated to give 1.1 g (65%) of **22** as a light pink solid: mp 158−160 °C. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ 5.79 (s, 2H), 6.45 (s, 2H), 7.49 (s, 2H); ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 98.7, 101.3, 139.6, 140.9; HRMS calcd for $C_7H_6O_4$ 154.02661, found 154.02670.

4-Methylbenzo[1,3]dioxle-5-ol (25). Methoxymethyl chloride (4.4 g, 55 mmol) was added slowly to a solution of sessamol (**3**, 5 g, 36 mmol) and diisopropyl ethylamine (7.6 mL, 44 mmol) in dry dichloromethane (20 mL) at 0 °C and the solution was warmed to 20 °C overnight. Water (10 mL) was added and the product was extracted with 3 × 30 mL of CH_2Cl_2), washed with 10% sodium hydroxide (15 mL) then with water (15 mL), and dried ($MgSO_4$). Removal of the solvent gave 6.5 g of an oil (6.5 g). This was used without further purification as described below. *n*-Butyllithium (19.4 mL, 1.7 M, 33 mmol) was added slowly to a solution of (5.0 g, 27 mmol) dry THF (20 mL) under nitrogen at −78 °C. The solution was maintained for 30 min. Methyl iodide (3.4 mL, 55 mmol) was added slowly at −78 °C and the mixture was allowed to warm to 0 °C over 2 h. The product was extracted with ethyl acetate (3 × 30 mL), washed with water (20 mL), and dried ($MgSO_4$) and the solvent was evaporated to give a brown oil (7.6 g). This oil was dissolved in methanol (100 mL) and treated with concentrated hydrochloric acid (0.5 mL). The solution was heated to 62 °C for 1 h and washed with saturated sodium bicarbonate. The product was extracted with ethyl acetate, washed with water, and dried ($MgSO_4$) and the solvent was evaporated to give a solid. Silica gel chromatography with ethyl acetate as eluent gave **25** as a pink solid (3.5 g, 83%): mp 95−96 °C. ^{1}H NMR ($(CD_3)_2CO$, 50 MHz) δ 2.05 (s, 3H), 5.86 (s, 2H), 6.26 (d, J = 8 Hz, 1H), 6.46 (d, J = 8 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 8.9, 101.4, 105.6, 106.5, 108.3, 140.8, 147.5, 151.5; HRMS calcd for $C_8H_8O_3$ 152.047345, found 152.04880.

4-Methylbenzo[1,3]dioxle-5,6-diol (24). The oxidation of **25** with Fremy's salt and subsequent reduction with sodium dithionite was carried out as with the formation of **22**. The yield of **24**, a light pink solid (mp 100−101 °C) was 78%. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ 2.08 (s, 3H), 5.78 (s, 2H), 6.32 (s,1H), 6.85 (s, 1H), 7.76 (s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 9.2, 95.9, 100.9, 108.7, 138.4, 139.1, 139.8, 139.9; HRMS calcd for $C_8H_8O_4$ 168.04226, found 168.04109.

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Supporting Information Available: ^{13}C NMR spectra and assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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